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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,413	01/09/2006	Guy Sauvageau	765/12810.191	5322

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EXAMINER	
HIBBERT, CATHERINE S	

ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
12/04/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/530,413	SAUVAGEAU ET AL.	
	Examiner	Art Unit	
	CATHERINE HIBBERT	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9,11-15,17-24,26-31,33,35-39,41-43,45 and 46* is/are pending in the application.

4a) Of the above claim(s) *1,9,11-15,17-24,26-30 and 41-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31, 33, 35-39 and 45-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/17/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants Amendment to the Claims filed 22 July 2009 was received and entered. This US Application 10/530,413, is a National Stage Entry of PCT Application PCT/CA2003/001539, filed on 6 October 2003, which claims priority to U.S. Provisional Application 60/416,545, filed on October 8, 2002. Claims 45-46 are new. Claims 2-8, 10, 16, 25, 32, 34, 40 and 44 are cancelled. Claims 1, 9, 11-15, 17-24, 26-31, 33, 35-39, 41-43, 45 and 46 are pending. Claims 1, 9, 11-15, 17-24, 26-30 and 41-43 are withdrawn. Claims 31, 33, 35-39 and 45-46 are under examination in this action.

Claims 1, 9, 11-15, 17-24, 26-30, and 41-43 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 21 November 2008.

Information Disclosure Statement

The submission of citation 5, Bhardwaj et al, listed on the information disclosure statement filed 17 August 2005 is acknowledged and the reference considered.

Response to Amendment/Arguments

Any objections/rejections not explicitly repeated herein are withdrawn.

New grounds of rejection necessitated by amendment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31, 33, 37-39 and 45-46 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Buske et al in "Deregulated expression of HOXB4 enhances the primitive growth activity of human hematopoietic cells" (Blood, 1 August 2002, Vol.,100, No:3, pp. 862-868, of record), and further in view of Krosl et al in

"Cellular proliferation and transformation induced by HOXB4 and HOXB3 proteins involves cooperation with PBX1" (Oncogene 1998, Vl 16, pages 3403-3412).

Currently amended Claims 31 and 33 are directed to a method comprising: treating stem cells with an effective amount of a stem cell expansion factor for a time sufficient to allow expansion of the stem cells, the factor comprising a blocker which reduces the expression level of at least one PBX gene, whereby reducing expression level of the PBX gene enhances expansion of stem cells containing (and thus "treated" with) a HOXB4 peptide. Claims 37/38 specify within Claim 31 that said stem cells are hematopoietic stem cells/human hematopoietic stem cells.

New Claims 45 and 46 specify that the blocker is a nucleic acid sequence (an antisense DNA to PBX1) blocking the expression of the PBX gene.

Buske et al teach treating human hematopoietic stem cells with a HOXB4 peptide encoded by a HOXB4 nucleotide sequence (e.g. abstract and Figure 1 and legend). Buske et al teach retroviral-mediated gene transfer was used for transduction experiments, in vitro (e.g. page 863, paragraph headed: "Retroviral constructs" and page 864, paragraph headed "Retroviral transduction of HOXB4 in human Lin- CB"). In addition, Buske et al contemplate inhibition/blocking/mutating of the PBX gene to promote stem cell amplification by HOXB4, state that the "mechanisms that lead to the differential gene effect are not known, but data points to a pivotal role of the TALE homeobox genes and Hox cofactors Meis1 and Pbx1 for the specification of Hox gene effects in the hematopoietic system" and further state "[i]mportantly, HOXB4 cannot

interact directly with Meis1 but only with Pbx1" (page 867, right column, paragraph 1).

In addition, Buske et al state:

> Our data characterize *HOXB4* as a potentially powerful positive mediator of the maintenance and expansion of human stem cells and provide a new avenue to manipulate and further elucidate the basis for human hematopoietic stem cell fate decisions. These in vitro and in vivo models will facilitate the dissection of the molecular mechanisms underlying the *HOXB4*-induced stem cell proliferation in the human cellular milieu. Furthermore, they will allow tests of whether stem cell amplification by *HOXB4* can be further augmented by mutating distinct motifs of the gene such as the PBX YPWM interacting motif as reported previously in the murine system[32]. [page 867, right column, paragraph 3]

Reference citation number 32, reported by Buske et al (just above) is cited in Buske et al on page 868, right column as "Beslu N, Krosl J, Humphries RK, Sauvageau G. Pbx1 is a negative regulator of Hoxb4-induced stem cell proliferation [abstract]. Blood. 2001; 98:451a" .

Buske et al fail to explicitly teach the stem cell expansion factor is a blocker comprising a blocker which reduces the expression of at least one PBX or specifically that the blocker is an antisense DNA to PBX1 gene.

Krosl et al teach administering an antisense DNA to PBX1 in conjunction with treating cells with HOXB4 peptide, *in vitro*, in Rat cells (e.g. page 3409, right column, paragraph 2).

One of ordinary skill in the art would have been motivated and found it obvious to have combined the methods of Buske et al with the antisense DNA to PBX1 of Krosl et al because Buske et al state that the "mechanisms that lead to the differential gene effect are not known, but data points to a pivotal role of the TALE homeobox genes and Hox cofactors Meis1 and Pbx1 for the specification of Hox gene effects in the

hematopoietic system" and further state "[i]mportantly, HOXB4 cannot interact directly with Meis1 but only with Pbx1" (page 867, right column, paragraph 1). In addition, Buske et al state:

> Our data characterize *HOXB4* as a potentially powerful positive mediator of the maintenance and expansion of human stem cells and provide a new avenue to manipulate and further elucidate the basis for human hematopoietic stem cell fate decisions. These in vitro and in vivo models will facilitate the dissection of the molecular mechanisms underlying the *HOXB4*-induced stem cell proliferation in the human cellular milieu. Furthermore, they will allow tests of whether stem cell amplification by *HOXB4* can be further augmented by mutating distinct motifs of the gene such as the PBX YPWM interacting motif as reported previously in the murine system[32]. [page 867, right column, paragraph 3]

Reference citation number 32, reported by Buske et al (just above) is cited in Buske et al on page 868, right column as "Beslu N, Krosl J, Humphries RK, Sauvageau G. Pbx1 is a negative regulator of Hoxb4-induced stem cell proliferation [abstract]. Blood. 2001; 98:451a" . In addition, Krosl et al teach administering an antisense DNA to PBX1 in conjunction with treating cells with HOXB4 peptide, *in vitro*, in Rat cells (e.g. page 3409, right column, paragraph 2).

Absent evidence to the contrary, one would have a reasonable expectation of success using the antisense Pbx1 of Krosl et al because Krosl et al demonstrate the use of the Pbx1 antisense for in vitro cell experiments using Hoxb4 peptides.

Response to Amendment/Arguments: Applicants Amendment to the Claims filed 22 July 2009 specifically regarding the addition of the limitation "said factor comprising a blocker which reduces the expression level of at least one PBX gene" in currently amended base Claim 31, has overcome the standing rejection under **35 U.S.C. 102 (a)** as anticipated by Buske et al. The comments regarding the Buske et al

reference regarding the previous rejection under **35 U.S.C. 102 (a)** in Applicants REMARKS filed 22 July 2009 are unpersuasive regarding the new grounds for rejection presented herein under **35 U.S.C. 103 (a)** for the following reasons:

Applicants argue that Buske *et al.* "does not teach the claimed method for enhancing expansion of stem cells which comprises treating stem cells with an effective amount of a stem cell expansion factor comprising a blocker which reduces the expression level of at least one PBX gene, whereby reducing the expression level of said PBX gene enhances expansion of stem cells containing a HOXB4 peptide" because Applicants argue that "Buske *et al.'s* abstract, Figure 1 and Figure 1 legend referred to by the Examiner describe or show the overexpression of HOXB4 induced by retroviral gene transfer in primitive human cord blood cells" and argue it "does not show the use of a factor which comprises a blocker for reducing the expression of a PBX gene".

While Buske et al fails to explicitly teach the newly added limitation "said factor comprising a blocker which reduces the expression level of at least one PBX gene", Krosl et al (above) teach administering an antisense DNA to PBX1 in conjunction with treating cells with HOXB4 peptide, *in vitro*, in Rat cells (e.g. page 3409, right column, paragraph 2) (above).

In view of the foregoing, the method of claims 31, 33, 37-39 and 45-46, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Thus, the claims are properly rejected under 35 USC *§103(a)*.

Claims 31, 33 and 35-36 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Buske et al in view of Krosl et al, as applied to Claims 31 and 33 above, and further in view of Largman et al (US Patent No. 5,837,507, of record) in view of Frankel et al (US Patent No. 5,804,604, of record).

Claims 31 and 33 are described above and are anticipated by Buske et al in view of Krosl et al for reasons applied above.

Claim 35 specifies within Claim 33 that the HOXB4 peptide comprises an HIV-derived peptide able to cross a cell membrane. Claim 36 specifies within Claim 35 that said HIV-derived peptide consists of a NH2-terminal PTD from a transactivating protein.

Although Buske et al teach retroviral vectors to transduce HOXB4 into human stem cells (above), Buske et al **fail to explicitly teach** that the HOXB4 peptide comprises an HIV-derived peptide able to cross a cell membrane or more specifically that the HIV-derived peptide consists of an NH_2-terminal PTD from a transactivating protein.

Largman et al teach the expression of an exogenous HOX gene, preferably HOXB4, in a stem cell to generate expanded populations of pluripotent stem cells *in vitro or in vivo* (e.g., Abstract; column 2, lines 35-59; column 8, lines 5-38; column 11, line 53 to column 12, line 50). The preferred stem cell is a hematopoietic stem cell, such as a human hematopoietic stem cell expressing the cell surface marker CD34 (e.g., column 2, lines 48-59). Largman et al teach that it is the expression of the HOXB4 gene (i.e., the HOXB4 protein) that results in the desired function (e.g., column 12, lines 5-37).

Largman et al **fail to explicitly teach** that the HOXB4 peptide comprises an HIV-derived peptide able to cross a cell membrane or more specifically that the HIV-derived peptide consists of an NH_2-terminal PTD from a transactivating protein (i.e. an HIV-TAT peptide).

Frankel et al teach the delivery of biologically active proteins to the cytoplasm and nuclei of cells *in vitro and in vivo* by the use of HIV-derived peptides able to cross a cell membrane, and specifically teach that these HIV-derived peptides consist of an NH_2-terminal PTD from a transactivating protein (i.e. an HIV-TAT peptide), which are covalently attached to the cargo protein (i.e. the protein of interest to be transported) (e.g., Abstract; column 1, lines 20-40; column 2, line 64 to column 4, line 3; column 7, lines 23-38). Frankel specifically teach the delivery of a transcription factor by TAT mediated protein transduction (e.g., column 12, lines 25-40). Further, Frankel et al teach that methods of DNA delivery typically deliver the nucleic acid molecules into only a fraction of the total cell population and tend to damage large numbers of cells (e.g., column 1, lines 54-63). In contrast, the methods of using the TaT protein to deliver proteins provide efficient delivery of non-tat proteins that are not inherently capable of entering target cells or nuclei, or are not inherently capable of entering cells at a useful rate (e.g., column 3, lines 6-15).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of generating expanded populations of stem cells of Buske et al in view of Krosl et al and further in view of Largman et al to replace the delivery of HOXB4 protein by delivering a nucleic acid molecule with the delivery of

HOXB4 protein by delivering a TaT-conjugated protein as taught by Frankel et al because Largman et al teach it is within the ordinary skill in the art to use HOXB4 protein expression to expand populations of stem cells and Frankel et al teach the delivery of proteins to cells *in vitro* and *in vivo*.

One would have been motivated to make such a modification in order to receive the expected benefit of more efficiently delivering the HOXB4 protein to the nucleus of the cells as taught by Frankel et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

In view of the foregoing, the method of claims 31, 33 and 35-36, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Thus, the claims are properly rejected under 35 USC *§103(a).*

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of objection/rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CATHERINE HIBBERT whose telephone number is (571)270-3053. The examiner can normally be reached on M-F 8AM-5PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully submitted,

Catherine S. Hibbert
Examiner/AU1636

/ Christopher S. F. Low /
Supervisory Patent Examiner, Art Unit 1636